Applicants thank Examiner Duffy for the helpful telephone interview of December 12 with Jean Duvall, inventor Peter A. Seubert and the undersigned attorney.

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. The Rejection

Claims 42-47 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants request reconsideration.

The Examiner rejected the claims on many grounds. In summary, the Examiner asserted that:

(1) The specification does not provide sufficient direction for a person skilled in the art to carry out the screening assay. For example, the Examiner alleged that the specification does not show how to get a test compound across the blood brain barrier; does not show how to obtain sufficient CSF sample size from small animals, such as mice; and does not indicate the timing of administration and testing.

(2) The current model systems for Alzheimer's disease are inadequate for screening compounds according to the method of the invention because none of the models exhibits all the histopathological and neuropsychological aspects of human Alzheimer's disease.

(3) Even if compounds are identified in the screen that alter the amount of $A\beta(x-\geq 41)$ in the CSF, there is no guarantee that such compounds would have the same effect in humans; or, if compounds identified in the screen prove to increase the amount of $A\beta(x-\geq 41)$ in the CSF of humans, there is no guarantee that such compounds would have an effect on mental state.

(4) The specification fails to teach how to make and use transgenic animals having expression cassettes for expressing the Swedish mutation of βAPP. For example, one may not be able to distinguish the Swedish version from the animal wild type.

(5) The specification fails to teach how to detect $A\beta(x-\geq 41)$ without using an antibody that spans the junction region.

In addressing the Examiner's concerns, it will be helpful to discuss the nature of the invention. Applicants

believe that the Examiner is applying too strict a standard for enablement in light of the invention to which the claims are directed.

B. The Nature Of The Invention And The Proper Standard For Determining Enablement

The claims are directed to methods for screening compounds for their ability to alter the amount of $A\beta(x-\geq 41)$ in the CSF. These methods permit one to identify candidate compounds for further testing and to compare the effect a compound has on $A\beta(x-\geq 41)$ levels in the CSF with its effect on histopathology. Applicants are not claiming the compounds that test positive in the screen--the claims are directed to methods of screening. Nor do Applicants assert that every compound testing positive in the screen will be a therapeutic drug for preventing or curing Alzheimer's. However, every advance in the understanding of the biology of Alzheimer's disease, and every tool that enables such advances, brings us closer to this end. The screening methods of the invention provide such a tool. Therefore, it not appropriate for the Examiner to evaluate this invention using standards that may be appropriate for therapeutic inventions. Rather, the proper question for enablement is: Does the specification enable one to determine whether a compound affects the amount of $A\beta(x-\geq 41)$ in the CSF? From this viewpoint, the specification enables any person skilled in the art to make and use the invention.

C. The Specification Provides Sufficient Direction For A Person Skilled In The Art To Carry Out The Screening Assay

The Examiner asserted that the specification did not provide sufficient direction to carry out the screening assays of the invention. Applicants traverse. A specification is enabling if a person skilled in the art can carry out the invention without undue experimentation. The examples identified by the Examiner are merely experimental parameters easily determined by the skilled artisan. For example, the Examiner asserted that a

person skilled in the art would not be able to assure that a test compound crossed the blood-brain barrier. However, a person skilled in the art would recognize that compounds known to cross the blood-brain barrier are preferred candidates for testing in the assay. Ascertaining whether a test compound can cross the blood-brain barrier is routinely done in evaluating compounds as potential drug candidates. Furthermore, the Examiner has not shown why it is beyond the capacity of a skilled artisan to find an alternative route of administration, for example, direct injection into the brain.

The Examiner also stated that it may not be possible to obtain sufficient CSF from a mouse to carry out the assay. The specification shows the detection of $A\beta(x-\geq 41)$ in animals as small as guinea pigs. Furthermore, as evidence that the method can be carried out on mice, Applicants submit herewith the Declaration of Peter A. Seubert under 37 C.F.R. § 1.132. In his declaration, Dr. Seubert states that the detection methods described in the specification are sufficiently sensitive to detect $A\beta(x-\geq 41)$ in a CSF sample of about 5 μl obtained from a mouse. Alternatively, the fluid from different animals can be pooled, each animal contributing a small amount to the sample.

The Examiner stated that the specification does not provide schedules for timing of administration of the compound and testing. Choosing parameters for such variables is routinely done in the field of efficacy testing. The Examiner has not shown why the choice of testing over, for example, weeks vs. months requires undue experimentation.

In sum, even if the practice of the invention involves experimentation to select parameters for, e.g., timing, sample collection or choice of test agent, such parameters are routinely selected without undue experimentation by those skilled in the art.

D. Current Animal Models Are Useful For Determining Whether A Compound Alters The Amount Of Aβ(x-≥41) In The CSF

The Examiner stated that the specification does not enable one to practice the invention in an animal model of Alzheimer's disease. She expressed concern that insofar as current animal models do not fully recreate all aspects of human Alzheimer's disease, such as neuropsychological symptoms and certain aspects of patho-histology, they are inadequate for use in the methods of the invention. Applicants request reconsideration.

The method of this invention is directed to detecting changes in Aβ(x-≥41) levels in the CSF. Such changes reflect processing of βAPP. Therefore, it suffices if the animal models used in these methods process βAPP, whether or not they also exhibit changes in mental state. Accordingly, Applicants have amended the claims to indicate that the animal model exhibits cerebral deposition of Aβ. Support for this amendment can be found in the specification on page 3, lines 11-15, which refer to cerebral deposition of Aβ as a characteristic of Alzheimer's disease, as well as page 14, lines 24-34, which discusses the expected connection between plaque deposition and Aβ(x-≥41) levels in the CSF. Furthermore, one model system useful in the screening methods of the invention, the "PDAPP mouse" is characterized by cerebral Aβ deposition. See, e.g., D. Games et al. (1995) *Nature* 373:523, enclosed herewith. Thus, the specification enables one to use non-human animal models characterized by cerebral deposition of Aβ in the screening methods of the invention.

E. Enablement Does Not Require That Compounds Testing Positive In The Screen Also Have Activity In Humans Or Alter Mental State In Alzheimer's Disease

The Examiner asserted that the invention was not enabled because compounds that altered the amount of Aβ(x-≥41) in an animal were not assured to have the same effect on humans, or alter their mental state. Applicants traverse.

Such a rejection applies an overly harsh standard against the pending claims. The claims are directed to methods of screening compounds for their ability to alter the amount of Aβ(x-≥41) in a non-human animal model system. Therefore, the proper standard for enablement is whether the method does, in fact, allow identification of compounds that affect the amount of Aβ(x-≥41) in the CSF of the animal tested. Applicants have demonstrated above that the specification does enables one to do so. Applicants are not claiming that every compound testing positive in the screen will have the same effect in humans or even that decreasing the amount of Aβ(x-≥41) in the CSF will act as a treatment of Alzheimer's disease. These effects do not relate to enablement of the claimed invention and should not be included in any standard to evaluate enablement.

F. A Person Skilled In The Art Can Make Transgenic Animals Having Expression Cassettes For Expressing βAPP

The Examiner stated that the specification did not enable the production of transgenic animals harboring an expression cassette that expresses the Swedish variant of βAPP. The Examiner stated that the production of transgenic animals is not routine in the art and requires a high level of skill. The Examiner further stated that the generation of animals displaying β-amyloid deposits is unpredictable. Applicants traverse.

The invention is not directed to the production of transgenic mice that deposit β-amyloid, but to their use in the screening methods of the invention. Therefore, the availability of any such models demonstrates that the invention is enabled. Transgenic animals models that deposit β-amyloid already are known. See, for example, PCT/US92/11276 and Games et al., *supra*, which describe the PDAPP mouse, and K. Hsiao et al. (1996) *Science* 274:99 (enclosed), which describes a transgenic mice expressing the Swedish mutation.

The Examiner further stated that Applicants have improperly incorporated application 08/143,697 by reference. While Applicants do not agree that this incorporation is

improper, they have, nevertheless, deleted reference to this application.

The Examiner also questioned whether the Swedish variant of βAPP was distinguishable from the native animal version. It is. In the Declaration of Peter A. Seubert, referred to above, Dr. Seubert indicates that the human and murine forms of Aβ differ at their amino-terminal end and, consequently, are distinguishable in immunoassays.

G. A Single Antibody Suffices For Quantifying Aβ(x-≥41), A Sandwich Assay Is Not Necessary

The Examiner stated that the invention is not enabled for assays in which Aβ(x-≥41) does not contain the junction region. Applicants traverse.

Applicants draw the Examiner's attention to the specification, page 18, last full paragraph. It states there that the detection of Aβ(x-≥41) can be accomplished by any methods known in the art for detecting peptides, including suitable immunological methods employing a single antibody, such as radioimmunoassay using an antibody specific for ≥41 forms of Aβ, or single antibody ELISA methods. Such methods do not require a peptide spanning the junction region for predictable and reliable measurement of Aβ(x-≥41). The use of single antibody ELISA to quantitatively measure APP is also known in the literature. In particular, Van Nostrand et al., *Proc. Natl. Acad. Sci., U.S.A.*, (1992) 89:2551, at page 2552, second column, describes such an assay. Applicants provided a copy of this article with the information disclosure statement already submitted. Furthermore, a sandwich assay to detect Aβ(x-≥41) can employ antibodies directed to other parts of Aβ. For example, Athena Neurosciences currently tests samples in the PDAPP mouse using a sandwich assay that includes an antibody specific for Aβ(x-≥41) (i.e., directed to the C-terminus) and an antibody directed to the N-terminus of Aβ. Thus, antibodies directed against the junction region are not required for detecting Aβ(x-≥41) even in a sandwich assay. Therefore, Applicants request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 576-0200.

Respectfully submitted,

John R. Storella
Reg. No. 32,944

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
(415) 576-0200
Fax (415) 576-0300
JRS:

j:\athena\2120\2120.am1